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HEMATOLOGICAL ADJUSTMENT TO HIGH ALTITUDES

M. G. Ringenbach

Translation of: "L'Acclimatation Hématologique a l'Altitude," *Bordeaux Médical*, No. 17, November 1973, pp. 2769-2777.

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16. Abstract

In contradistinction to others, the author studied red blood corpuscle presence in both venous and capillary blood in relation to high altitudes and mountain sickness. He finds a three-phase adaptation of these corpuscles to high altitudes. He demonstrates that hematoporphyrine is useful in treating mountain sickness.

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HEMATOLOGICAL ADJUSTMENT TO HIGH ALTITUDES[1]

M. G. Ringenbach[2]

The present paper summarizes original research carried out over a period of twenty years. /2769*

It concerns what the author proposes to call "the second stage of adjustment of high altitudes," the first stage consisting of a short-term polyglobulia so fleeting that it is difficult to observe, and the third stage of real adjustment to altitude, namely long-term polyglobulia, such as exists in peoples who have lived for centuries at altitudes of between 3,000 and 5,000 meters (Indians of Andes regions).

The second stage of adjustment to altitude that Ringenbach was the first to describe could be studied with a "veno-capillary coupled erythrogram" technique which makes a "blood snapshot" possible. It is characterized by two phenomena: on the one hand, a reduction of red blood corpuscles especially in the venous blood, on the other hand an unequal division of these red blood corpuscles in the venous blood and the capillary blood, the difference of concentration being of the order of 30%.

Based on these observations, the author derived a chronology of this adaptation. Furthermore, he studied the pathology of disorders which characterize this second stage and showed that three mechanisms may explain it: hemolysis, isolation of the red blood corpuscles and perturbation of the water metabolism. The radio-isotopic method made it possible to refute the first two. The technique of measuring total blood and plasma volumes confirms the third.

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*Numbers in the margin indicate pagination in the foreign text.

Ringenbach finally suggests prophylaxis for disorders due to altitude adaptation by means of hematoporphyrine; this is a valuable remedy both by virtue of its effect on the nervous system and in combatting anemia. Thanks to it, astronomers, glaciologists, physicists, doctors, observatory maintenance personnel, explorers, etc., who live in high mountains, can live safely and comfortably.

Adjustment to altitude is a modern problem because of flights into space and because of the development of general aviation.

History

Reduction in atmospheric pressure and oxygen pressure in environmental air leads to hematosis insufficiency and various difficulties known from the works of Jourderet, Paul Bert (*Barometric Pressure*, 1878), Mosso, Barcroft, Haldane, Binet, and Harron. The idea of "altitude polyglobulia" seems to be due to Viault, who verified it on himself during a trip to Peru at the altitude of 4,392 meters. This is the name he used in 1907 to describe a significant increase in the red blood corpuscle ratio, reaching as much as 7 to 8 million per cubic millimeter. He attributed this phenomenon to the rarefaction of the air leading to a reduction in the oxygen pressure of the air. "In animals and men living at high altitudes the struggle for oxygen determines an exaggeration in red blood corpuscle manufacture, demonstrated by an increase in the number of red corpuscles and of hemoglobin, verified directly by counting and by colorimeter (Viault) and by iron dosage (Muntz)" [1]. /2770

This "long-term" polyglobulia, traditionally attributed to compensating proliferation of the red blood cell manufacturing organs, was later studied in Peru by C. Monge [2]. An entire people has lived for centuries on the high plateaus of the Andes Mountains, between 3,000 and 5,000 meters up. These Indians have a very remarkable appearance: their face is red, their mucous linings are highly colored, and they have the wide thorax of athletes and Hippocratic fingers and toes. Their physical and mental ability have been sometimes been considered normal (Monge), sometimes reduced (Barcroft). They have polyglobulia on the order to 7 to 8 million per cubic millimeter with the normal proportion of leucocytes. This polyglobulia is stable and almost always tolerated well [4].

Along with this chronic polyglobulia, an acute syndrome has been described under the name of "mountain sickness": polymorphic difficulties, occurring at the time of ascent and at the beginning of the high altitude state, polyuria, resting, working and decubitus dyspnea, precordialgia, insomnia, headache, asthenia, joint pains, digestive troubles, sometimes very accentuated nervous difficulties, and reduction of mental capacity. We observed redness in the face which becomes cyanic at the least effort, dilatation of the face veins, congestion of the buccal and conjunctive mucous linings, and sometimes splenomegaly. Here again Monge has described a so-called "short-term" polyglobulia with frequent reticulocytosis, increase in indirect bilirubinemia and moderate leukocytosis, and sometimes monocytosis.

During the French Himalayan expedition in 1950 Oudot verified an increase in hemoglobulin reaching 140/100 at 5,900 meters in one subject after a sojourn between 6,000 and 7,500 meters high. The oldest subject had a much less significant figure at 110/100 [3]. This research was made with Sahli's hemoglobinometer on blood taken from the pulpy part of the finger and not from the veins (this fact is important as will be shown later in this report).

All of the difficulties related to altitude disappear when the subject descends. But if he remains at high altitude fatal complications may occur: thromboses and nervous center hemorrhages, cardiac insufficiency, and syncope.

Monge has likened these high altitude problems with polyglobulia symptoms of the Vaquez type.

In concert with Fave in 1950 [5], and then in other publications, we have published the results of our research on pilots at altitudes from 4,000 to 9,000 meters for the purpose of checking the existence of this short-term polyglobulia and of specifying its mechanism. Our work, carried out only with venous blood at the time, in a Halifax bomber at 9,000 meters or in a moraine at 4,000 meters, did not and with confirming this theory since, on the contrary, we found a significant globular drop. At the time we even developed doubts about the existence of this polyglobulia. In addition even the confirmation of this phenomena required the perfection of man's immediate adaptation to the altitude. Now, this adaptation is far from being consistently realized, since a "mountain sickness" exists. Finally, we were struck by the

fact that work previous to ours had been mostly carried out on capillary blood, while we were operating with venous blood. Had not each of us, operating with different methods, recorded only part of the phenomenon? Could there not be an inequality in distribution of the red blood corpuscles, concentrated in the capillary blood and, at a normal or reduced ratio in the venous blood? Furthermore, was it not possible that this acclimatization to altitude could be carried out in a number of phases, leading to different findings?

Therefore we decided to study the phenomenon under real conditions, i.e., in people residing at high altitudes for variable lengths of time (not in animals because in this case such experimentation seemed very questionable to us); in addition we would make counts of globules in the venous blood and in the capillary blood at the same time using a method beyond any reproach.

Personal Research

Our technique for counting red blood corpuscles was described in 1951 [6]: the venous puncture with a dry syringe without the addition of anticoagulants, immediate sampling of the pure blood in the syringe with a pipette, and counting of the red blood corpuscles without delay. This method seems correct to us, in contradistinction to those which use a mixture of blood with various /2771
anticoagulants, the impropriety of which we have demonstrated by comparative studies, i.e., red blood corpuscle figures are sometimes provided 25-30% lower than the real figure! We have verified this fact numerous times, both in subjects who came to us to control grave anemia, nonexistent in reality, and on real patients and normal subjects. Let us specify that the error coefficient in our method is less than 2%.

The other condition, a variety in the age of our subjects and in the length of their life at high altitude, was achieved during several sojourns in observatories: in 1951 at the Jungfraujoch Alpine Station at an altitude of 3,454 meters [7, 8], and later in January, March and April 1967, January and July 1969, and July 1970 at the Pic du Midi Observatory at an altitude of 2,860 meters [9].

We were able to observe a total of 72 subjects, including the subjects of our experiments and ourselves. Their age ranged from 21 to 65, with the majority being less than 40 years old. By profession they were physicians,

glaciologists, astronomers, doctors, nurses, students, O.R.T.F. [Translator's note: Expansion unknown] agents, meteorologists, engineers, photographers, supervisors, mechanics, electricians, cooks, and service personnel. The length of their stay was extremely variable: 3-6 days for the majority, 8 days to 1 months for a third of the subjects, 4-6 months for four of them, and 18 years for the caretaker of the Jungfraujoch Station, 50 years old, with 3 days per month in flat country. The majority remain only 5-7 days at Pic du Midi, and then descend to flat land for 7-10 days because of the typical problems which altitude produces in most.

Here is a Summary of our Observations:

Clinically we have recorded an increase in the cardiac rate: tachycardia (80 to 96), elevation of arterial pressure, especially minima (on the average: maximum 15 to 16 cm Hg, minimum 10 to 11 per Vaquez), polypnea (average 25/min).

From the hematological point of view: our veno-capillary coupled erythrogram method, i.e., simultaneous calculation of the ratio of red blood corpuscles and of hemoglobin in venous blood and in capillary blood, has given us the following average results:

- venous blood: 3,800,000 red blood corpuscles/mm^3 in 80% of cases with extreme values of 2,900,000 in 10% of the cases and 4,500,000 in 10%;
- capillary blood: 4,600,000 red blood corpuscles/mm^3 in 90% of the cases, with extreme values of 3,400,000 in 6,600,000.

This is a difference of 22% in average concentration, with a maximum of 33%.

Each observation studied individually shows striking analogies with the others, although the subjects are of very different ages and have been at a high altitude for periods which are also extremely variable. In respect to our experimental subjects and ourselves, it is very remarkable to verify very quickly a divergence in the two slopes of total venous and capillary ratios. This ratio, quite similar at sea level, is reduced to 15-20% in the venous blood beginning with the second day at high altitude, while it is reduced much less or even increases in the capillary blood. The differences between the slopes reach as high as 30%, this ratio being far superior to that of the

errors in our method (2%). This divergence in the two slopes is maintained with a few fluctuations throughout the sojourn and is not attenuated until several hours after returning to flat land.

Therefore our veno-capillary coupled erythrogram method has allowed us to demonstrate a double phenomenon in the second phase of hematological adaptation to high altitude: on the one part the drop in red blood corpuscles, especially in the venous blood, and on the other the unequal distribution of these corpuscles in the venous blood and in the capillary blood, the difference in concentration being near 30%.

We believe we are the first to describe this double phenomenon which we consider to be a hematological criterion of adaptation to high altitude, one step toward the acclimatization realized in the third phase, which is nothing but true polyglobulia.

The following facts are produced by the entire complex of our observations: it seems that a high altitude sojourn varying from 5 days to several weeks does not produce real venous polyglobulia and that short-term high altitude polyglobulia has been observed only in capillary blood. It is this latter finding that seems to have been the only one recorded by a number of conscientious observers whose investigations were incomplete because they were /2772 limited to the capillary blood alone.

When, on the contrary, the length of a sojourn at high altitude varies from 1 to 6 months, we find that the average ratio of red blood corpuscles in the capillary blood lies between 5,700,000 and 6,600,000, with the venous blood having the concentration specified above.

These different values may correspond to successive stages in hematological adaptation to high altitude.

Although we have not been able to study the same subjects for several weeks at regular intervals in order to clearly demonstrate these various phases, it is possible for us to imagine the chronology of this adaptation as follows. It could be carried out in three stages of duration varying with the individual:

1. Immediately upon ascent: moderate "short-term", "fortuitous" to use H. Roger's expression, temporary polyglobulia related to the mobilization by

the organism of its reserve red blood corpuscles, in particular the splenic ones. The role of the spleen would be essential according to Binet who has shown that this organism contracts, perhaps under the influence of a discharge of adrenaline, and puts a large number of red blood corpuscles into circulation. The splenomegaly sometimes found by Monge at this stage is difficult to interpret, because it allows us to think of hemolysis, and the conclusion of this report shows contradictory facts.

Other reserve organs besides the spleen could also liberate a certain amount of red blood corpuscles.

This polyglobulia would be very brief and could only be demonstrated by examination repeated at brief intervals, which would explain why we have not been able to record it.

2. In the second place there would be a drop in red blood corpuscles in both the venous and capillary blood at the same time: this is exactly the phenomenon which we have noted in the majority of our subjects. The Swiss authors, Violette [Translator's note: This may be a misprint for bibliographic reference No. 1 Viault and Jolyet], have also found "an increase in destruction of red corpuscles and a paradoxical anemia during the first days at high altitude in the case of intense physical exercise." These findings agree with ours, and only the interpretation is different.

3. When high altitude sojourn varies from a few weeks to several months a true polyglobulia could become established, connected with the compensatory hyper-functioning of the blood producing centers (Monge). This phenomenon would be particularly demonstrated in young subjects, and would be reduced after a certain age (the case of the caretaker of the Jungfraujoch Observatory and findings of Oudot). It would be habitual among the Indians of the high plateaus of the Andes range and would show real acclimatization to high altitude, perhaps hereditary, while the first two phases would be concerned only with more or less good adaptation to new conditions of existence, truly aggressive actions of the organism.

Pathogenesis Of Difficulties in High Altitude Adaptation

Hematological adaptation to high altitude seems to us to be an individual problem which can be resolved only by a systematic study. Actually every subject can meet the aggression formed by high altitude sojourns in a number of ways. The reasons for individual resistances and sensitivities are not very well known: Monge has demonstrated a break in equilibrium between the number of red blood corpuscles and the ratio of atmospheric pressure, the lessening of pulmonary permeability to oxygen, the reduction in arterial saturation by oxygen, and by use of oxygen by tissues, all varying according to the individual. Harron [4] has shown that those who have a Krogh coefficient equal to or superior to 40/100 never suffer from mountain sickness. Severe incidents are seen in those below 30. On the other hand, subjects acclimated to high altitudes have a coefficient of 60 and get along as well as the inhabitants of the flat lands.

Grandjean has shown the importance of the perturbation of the vago-sympathetic system: most often sympathicotonia, sometimes vagotonia at the same time (miosis constancy), achieving Danielopolu's amphotonia; sometimes at the end of a few weeks there is pure vagotonia.

Study of the modifications of the oculo-cardiac reflex and of the arterial pressure allows us to make the following statements: the pulse is usually accelerated at high altitude. [Translator's note: the following sentence in French does not make sense, possibly because of a misspelling or a word or a phrase left out]. Compression of the eyeballs (ROC) slows it (pulse? itself?) down in half of the cases (vagotonia) or has no result (amphotonia). At high altitude arterial pressure is increased, particularly the minima (narrowing of the differential).

It seems reasonable to attribute the unequal distribution of red blood corpuscles to these phenomena which modify the tonus of the vessels in a spasm-like way in a consistent and lengthy manner. In fact the majority of our subjects, normal on low ground, showed an increase in arterial pressure at high altitude. The increase in the cardiac beat and in the respiratory rhythm, which we have noted, can be interpreted as compensatory phenomena for the drop in red blood corpuscles and for hypoxia, although the venous hypoglobulia does not occur until after a certain period of hypoxia. /2773

We have likewise noted in our original research [10] that there is a connection between the arterial hypertension and the irregular distribution of the red blood corpuscles at high altitude. In 27 cases of individual arterial hypertension we have found that the concentration of the red blood corpuscles is about 30% stronger in the capillary blood than in the venous blood, or the same proportion as at high altitude. After treatment the arterial pressure became normal and, at the same time, the globular ratio became the same in the venous and capillary blood. The treatment worked like a return to the low lands.

In order to explain the reduction in the red blood corpuscle ratios in the venous blood, three mechanisms seem possible:

1. Hemolysis, considered in 1930 by Monge, who observed indirect hyperbilirubinemia at high altitude.

Against this hypothesis we find the return of the venous and capillary globular ratios to normal upon descent to sea level, as observed by us; the statements of Blanquet, Ducassou and ourselves, using the radioisotope method (marking red blood corpuscles with Cr 51 and looking for possible hemolysis), and concluding that there is an absence of hemolysis at high altitude.

2. Sequestration of the red blood corpuscles from reservoir organs (liver, spleen). Here too, the radioisotope method used by the same authors has shown that this mechanism can not be maintained, since the radioactivity of the organs does not change.

Radioisotope study [17]: we made a measurement of the length of life of the red blood corpuscles (Cr 51) in 4 experimental subjects; examination, begun two days before their departure for the Pic du Midi Observatory (altitude: 2,860 meters), was continued throughout their stay at high altitude (4 days) and ended 2 days after their return to the lowlands; in addition a study of the radioactivity accumulated at the level of the liver and the spleen was made before and after the high altitude stay in order to demonstrate possible locations of destruction or sequestration of the red blood corpuscles. Finally the feces of the subjects were collected throughout the examination period in order to demonstrate possible digestive interference.

Method: The red blood corpuscles were marked by incubating 20 ml of the subject's blood for 30 minutes at 37°C on ACD with 50 μ of Ci of chromate (Cr 51). After injecting the subject with the marked red blood corpuscles, blood samples were taken on the first, second, fourth, sixth, seventh and nineth days. The result of the activity measurements made on 2 ml of blood from each of the specimens is recorded on semi-logarithmic paper and allows the biological half life of the red blood cells to be determined (normal: 25 to 30 days).

External measurement of the activity accumulated at the level of the liver and the spleen is referred to the radioactivity of the precordial region (normal: less than 1.7).

The radioactivity of the feces collected during the examination period is expressed in millimeters of blood lost per day (normal: less than 2 ml).

Results: these three pieces of research have produced tangibly normal results.

In the four experimental subjects the half life of the red blood corpuscles has been: 35 days, 25 days, 24.5 days and 16 days, or 3 normal results out of 4 subjects.

The radioactivity of the liver and of the spleen, referred to that of the precordial region, varied between 0.60 and 0.90, or within normal limits.

The radioactivity of the feces was also found to be normal in the four subjects (less than 2 ml per day).

3. Difficulties in water metabolism, or an increase in plasma volume, leading at the same time to arterial hypertension phenomena and to a drop in red blood corpuscles in the venous blood.

This is the mechanism we were able to demonstrate in three subjects during a second sojourn (December 1971) at the Jungfraujoch Alpine Station (altitude: 3,500 meters) by using the method of measuring total and plasma blood volumes with polyvinyl pyrrolidone (Subtosan 25). /2774

According to the method described by Labadie in his thesis [18] and by Poulain and Piette [19]: 5 ml of PVP 25 Specia, or 1.25 grams, are injected

into a vein at the bend of the elbow. Four minutes later 10 to 15 ml of blood are taken from a vein in the other arm; after centrifuging and noting the hematocrit, some plasma is taken, supplemented with NaOH (defecation) and SO4Zn, filtrated, and supplemented with a Lugol solution. The colorimetric reaction obtained is evaluated by photometry (490 λ filter). Its intensity is proportional to the plasma concentration. Knowing this plasma concentration and the hematocrit ratio, we can deduce the plasma volume, the total blood volume and the red blood corpuscle volume.

Results: Pulse acceleration, increase in arterial pressure, and positive oculo-cardiac reflex giving evidence of a state of sympathicotonia beginning with the fifth hour of the high altitude sojourn; the same investigations are made at the 24th hour. The red blood corpuscle ratio is reduced by 12 to 25% in the venous blood, from 0 to 8% in the capillary blood, and the hematocrit of the venous blood is reduced by 5 to 10%; the total blood volume is reduced by 10 to 13%, and the plasma volume is unchanged.

In interpreting these figures and in keeping in mind the fact that the modifications described are individual and variable in direction, chronology and intensity, it is possible to think that the hematological adaptation mechanism which we have described includes two essential time periods:

- during the first hours of the high altitude sojourn, we have increase in plasma volume and, as a consequence, false anemia caused by dilution of the venous blood (reduction of the ratio of the red blood corpuscles and of the hematocrit);

- after 24 hours, in correlation with the arterial hypertension and the oculo-cardiac reflex + (sympathicotonia), we have a reduction in total blood volume. As a mater of fact Labadie has pointed out a reduction in total blood volume in arterial hypertension.

Therefore the plasma hypervolemia would be produced from the beginning of the high altitude sojourn. At first absolute, it would then become relative because of the secondary reduction of total blood volume. The phenomena of high altitude hematological adaptation, which we have described, would therefore be due to problems in water metabolism, themselves dependent on hypoxic sympathicotonia.

Prophylaxis For High Altitude Adaptation Difficulties

No matter what the origin of these problems produced in high altitude adaptation, is not the important thing for a doctor to find a treatment for them in order to allow acceptable life under new conditions? The therapeutic aspect of these difficulties does not seem to have been the object of systematic research, and still is certainly important to improve the mode of existence of those who live in high mountain country.

We believe that hematoporphyrine, of which we have made an original study [11, 12, 13, 14, 15], may be the proper remedy, both because of its action on the nervous system and because of its role in combatting anemia.

On the one hand this product is actually known for its tonic, stimulating and euphoric action, as a regulator of the vegetative nervous system, and in the treatment of melancholic states and depressive psychosis. It appears to have no effect on arterial pressure.

On the other hand we have shown from 120 observations that hematoporphyrine has a rapid and significant action in a large number of anemias, in particular nutritional macrocytic anemias. Orial administration of this product for 20 days has been followed by an increase in red blood corpuscles on the order of 1 million per cubic millimeter, by an increase in hemoglobin by 4%, of hematocrit by 2%, and reticulocytes by 150,000 per cubic millimeter, and by a reduction in the globular value by 0.3 and in the average globular volume by 28.3 μ. The macrocytes from the beginning of the treatment have been progressively replaced by red blood corpuscles of a more normal form, significant reticulocytosis being shown by hyperactivity of the marrow.

A radioisotope study [15] has allowed us to demonstrate the selective fixation of the hematoporphyrine marked by Cu 54 and Co 57 and 58 in the marrow and, especially, in the liver and kidneys. It seems that the role of the hematoporphyrine in combatting anemia is not direct, and that erythroblastic differentiation takes place through the intermediary of erythropoietin. The use of this product to prevent high altitude adaptation difficulties has given us remarkable results. /2775

As a matter of fact the hematophorphyrine has made it possible for us to correct the two phenomena which, according to our work, characterize the second phase of high altitude adaptation: we have shown that administration of this product increases the ratio of the red blood corpuscles in the venous blood up to a subnormal value and makes their concentration in the venous blood and in the capillary blood tangibly identical.

In order to obtain this result we administered hematoporphyrine to 6 subjects for 19 to 20 days, a period including 5 days of high altitude at the Pic du Midi (altitude: 2,860 meters), 10 days in the lowlands and 4 to 5 days at the Pic du Midi altitude. This was when we were able to achieve in each subject a venocapillary coupled hemogram according to our method. Comparison of the globular ratios obtained in this way with those recorded 3 months earlier with the same subjects and under the same conditions, i.e., on the 4th or 5th day of stay at Pic du Midi but without hematoporphyrine preparation, is very characteristic. On the average the figures obtained were as follows:

- after treatment (27 January 1967):
  capillary blood: 4,200,000 red corpuscles,
  venous blood: \3,300,000 red corpuscles;
- after treatment with hematoporphyrine (22 April 1967):
  4,000,000 and 3,900,000 respectively.

In accord with this hematological transformation our 6 volunteers admitted to considerable subjective improvement: on the whole they were less fatigued by the altitude, capable of actions which were impossible for them during previous sojourns, their appetite and sleep were better, and their headaches were very reduced.

Although this series only includes 6 observations, it is remarkable to find such agreement.

In addition, in confirmation of our work, Feliho has shown in his thesis [16] that after administration of hematoporphyrine resistance of the guinea pig to hypoxia is considerably increased.

Therefore we believe it is legitimate to hope that the systematic administration of hematoporphyrine during the 3 weeks preceding a high altitude sojourn will be able to eliminate adaptation problems.

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